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Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature

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Abstract Severe intraventricular hemorrhage caused by extension from subarachnoid hemorrhage or intracerebral hemorrhage leads to hydrocephalus and often to poor outcome. We conducted a systematic review to compare conservative treatment, extraventricular drainage, and extraventricular drainage combined with fibrinolysis. We carried out a search in Medline of the literature between January 1966 and December 1998 and an additional hand-search from January 1990 to December 1998. Pharmaceutical companies were contacted to gather unpublished data. We reviewed the reference lists of all relevant articles. Two authors independently assessed eligibility of the studies and extracted data on characteristics of study design, patients, and treatment. Patients with primary intraventricular hemorrhage were excluded. Main outcome measures were death and poor outcome (defined as death or dependency) at the end of follow-up. No randomized clinical trial has yet been conducted so far, and we therefore reviewed only observational studies. The case fatality rate for conservative treatment (ten studies) was 78%. For extraventricular drainage (seven studies) it was 58% [relative risk versus conservative treatment (RR) 0.74; 95% confidence interval (CI) 0.55–0.99]. For extraventricular drainage with fibrinolytic agents (five studies) the case fatality rate was 6% (RR 0.08; 95% CI 0.02–0.24). The poor outcome rate for conservative treatment was 90%, that for extraventricular drainage 89% (RR 0.98; 95% CI 0.75–1.30) and that for extraventricular drainage with fibrinolytic agents 34% (RR 0.38; 95% CI 0.21–0.68). All RR values remained essentially the same after adjusting for age, sex, World Federation of Neurological Surgeons scale, study design, and year of publication for the studies that provided these data. Outcome is thus poor in patients with intraventricular extension of subarachnoid or intracerebral hemorrhage. This meta-analysis suggests that treatment with ventricular drainage combined with fibrinolytics may improve outcome for such patients, although this impression is derived only from an indirect comparison between observational studies. A randomized clinical trial is warranted.

Key words Intraventricular hemorrhage · Subarachnoid hemorrhage · Intracerebral hemorrhage · Extraventricular drainage · Fibrinolysis

Introduction

Intraventricular hemorrhage (IVH) is a frequent complication of subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). The severity of IVH varies from sedimentation of blood in the posterior horns to complete filling of all ventricles. Massive IVH has been associated with a poor outcome [5, 10, 16, 21, 25]. IVH often leads to acute hydrocephalus, which can be treated by means of lumbar puncture or extraventricular drainage (EVD) [6, 15]. Lumbar puncture is not warranted when there is massive IVH, and EVD is often hampered by obstruction of the drain because of blood clotting. The risk of drain obstruction may lead to a nihilistic approach. In recent years some studies have described fibrinolytic treatment in combination with EVD to prevent drain obstruction. The results seem favorable compared with no treatment, but all studies have an observational design, and most include only small numbers of patients. No randomized clinical trial (RCT) has yet been conducted. Therefore we performed a systematic review of observational studies to compare no treatment, EVD, and EVD plus fibrinolytic therapy.

Materials and methods

Identification of studies

To identify studies on treatment and outcome after severe IVH we first performed a Medline search from 1966 onward. Secondly, we hand-searched 11 neurological and neurosurgical journals from January 1990 to December 1998. We then scrutinized the reference lists of all relevant publications for additional studies. The references of the publications thus found were checked again for additional studies. This method of cross-checking was continued until no further publications were found. To retrieve unpublished data we contacted five pharmaceutical companies that produce fibrinolytic agents.

Eligibility of studies

Two authors independently assessed the eligibility of the studies using predefined inclusion criteria. These criteria were: (a) Diagnosis of IVH was by computed tomography. (b) The IVH was severe; if possible, we selected patients with a score of 7 or higher on the Graeb et al. scale [5]. This scale adds the individual scores (maximum 12) for the lateral ventricles (1, trace of blood or mild bleeding; 2, less than half of the ventricle filled with blood; 3, more than half of the ventricle filled with blood; 4, ventricle filled with blood and expanded) and the third and fourth ventricles (1, blood present, ventricle size normal; 2, ventricle filled with blood and expanded). If no Graeb et al. score was given, we accepted studies on patients with complete hematocephalus and patients with IVH classified as severe by the authors. (c) The case fatality rate was given. (d) Patients with primary intraventricular hemorrhage were excluded because these have a better prognosis [20]. If only an overall case fatality rate was calculated, at least 90% of the cases with IVH were caused by SAH or ICH. (e) At least five patients matched the criteria in the study.

Data collection

After the initial assessment for eligibility, two authors independently extracted the following data from the included studies: year of publication, study period, study design (prospective or retrospective), number of patients, percentage of men, mean age, cause of IVH (SAH, ICH or other), neurological condition of the patients on admission (World Federation of Neurological Surgeons scale [3] (WFNS scale) divided into two categories: 1–3 versus 4 or 5), severity of IVH, method of treatment (conservative, EVD, or EVD with fibrinolytic agents), treatment characteristics and complications, posttreatment outcome, and cause of death. If possible, we excluded patients with causes other than SAH or ICH. Studies were classified as prospective if this was explicitly noted in the article, or if this was unequivocal from the body of the text. If the Glasgow Coma Scale (GCS), Reaction Level Scale 85 (RLS 85), or a preoperative neurological grading system was used to describe neurological condition, we converted this into a WFNS grade. The outcome was classified in two ways: proportion of deaths and proportion of patients with poor outcome (death or dependent). We defined dependent as having Glasgow Outcome Scale (GOS) score of 3 or 2 [24] or a modified Rankin score of 4 or 5 [26]. Patients with an outcome reported as "fair," "moderate disability," or "partly dependent" were considered independent. Patients who were in a rehabilitation facility at the time of outcome assessment were scored as dependent.

If the two independent authors disagreed on extracted data, they reviewed the data together to reach consensus.

Data analysis

We calculated the case fatality rate and poor outcome rate for each of the three treatment strategies. We then calculated the raw risk ratio (RR) with corresponding 95% confidence interval (CI) for EVD and EVD with fibrinolysis by means of univariate Poisson regression, with conservative treatment as reference. We adjusted the RR for year of publication, mean age, study design, percentage of men and percentage of patients with poor WFNS grade of baseline to address possible incomparabilities between the treatment groups. We defined poor outcome as Rankin grade 4 or 5. We also performed a sensitivity analysis with poor outcome defined as Rankin grade 3, 4, or 5. Finally, we performed similar analyses in the subgroups of patients with SAH and patients with ICH to determine whether the treatment effects differed between the two groups.

Results

As no randomized clinical trial has been conducted so far, we reviewed only observational studies. We identified 18 articles published between 1980 and 1998 that fulfilled our inclusion criteria (Table 1), including a total of 343 patients. Fourteen of these studies assessed only a single treatment strategy: eight conservative treatment, three EVD, and three EVD combined with fibrinolytic agents. Four studies compared two treatment strategies: two EVD and conservative treatment (nonrandomized) [22, 23], one EVD and EVD combined with fibrinolysis (nonrandomized) [2], and one EVD combined with fibrinolysis and a historical control group treated by EVD [18]. Ten studies were retrospective, seven were prospective, and one used a retrospective control group and a prospective intervention group [18]. Eight reported the sex of the patients;

Table 1 Overview of studies with data on treatment of intraventricular hemorrhage

Study	*n*	Cause	Design	Mean age (years)	Sex (% male)	WFNS (% 4/5)	Death (*n*)	Poor outcome (*n*)
Conservative								
Pia (1980) [17]	9	SAH	Retrosp.	–	–	–	9	9
	8	ICH	Retrosp.	–	–	–	8	8
Ikeda et al. (1982) [9]	16	SAH	Retrosp.	–	–	–	11	–
	21	ICH	Retrosp.	–	–	–	16	–
Mayr et al. (1983) [14]	20	ICH	Retrosp.	–	–	–	17	18
Matsumoto and Hondo (1984) [12]	7	ICH	Prosp.	64	100	71	0	4
Ruscalleda and Peiro (1986) [21]	21	ICH	Retrosp.	–	–	–	17	–
Pasqualin et al. (1986) [16]	39	SAH	Retrosp.	–	–	–	38	38
Steinke et al. (1987) [23]	4	SAH	Retrosp.	–	–	–	1	2
Lu (1989) [11]	14	ICH	–	–	–	–	7	–
Shapiro et al. (1994) [22]	4	SAH	Retrosp.	58	50	25	2	2
	2	ICH	Retrosp.	75	50	100	2	2
Roos et al. (1995) [20]	11	SAH	Retrosp.	58	–	100	11	11
EVD								
Steinke et al. (1987) [23]	11	SAH	Retrosp.	–	–	–	6	8
Hayashi et al. (1988) [7]	44	ICH	Prosp.	–	–	–	21	38
Hayashi et al. (1989) [8]	24	SAH	Prosp.	–	–	–	14	24
Shapiro et al. (1994) [22]	11	ICH	Retrosp.	58	64	82	8	10
	7	SAH	Retrosp.	48	29	86	7	7
Akdemir et al. (1995) [2]	6	ICH	Prosp.	56	0	100	5	5
	1	SAH	Prosp.	57	100	100	0	1
Rainov and Burkert (1995) [18]	5	ICH	Retrosp.	53	60	100	1	3
Adams and Diringer (1998) [1]	9	ICH	Retrosp.	60	33	100	7	9
EVD + fibrinolysis								
Findlay et al. (1993) [4]	7	SAH	Prosp.	49	57	71	0	1
Mayfrank et al. (1993) [13]	10	ICH	Prosp.	64	50	90	0	–
	1	SAH	Prosp.	68	100	100	0	–
Akdemir et al. (1995) [2]	7	ICH	Prosp.	61	43	100	2	2
Rainov and Burkert (1995) [18]	12	ICH	Prosp.	57	50	100	0	0
	1	SAH	Prosp.	58	100	100	0	1
Rohde et al. (1995) [19]	7	SAH	Prosp.	53	43	100	0	6
	4	ICH	Prosp.	61	75	75	1	3

51% were men. Age was given in nine studies; mean age was 58 years. Nine studies provided the WFNS score; in these studies 88% of patients were in poor clinical condition (grade IV or V).

The outcome for all patients and for the subgroups of patients is given in Table 2. The RR for EVD with fibrinolysis compared with EVD without fibrinolysis was 0.10 (95% CI 0.03–0.33) for case fatality and 0.38 (95% CI 0.22–0.68) for poor outcome. Adjusting the RR for year of publication, study design, mean age, percentage of men, and percentage of patients with poor WFNS on admission yielded essentially the same results; these analyses could be performed for only a subset of all studies because of lack of data from several studies. In all these analyses poor outcome was defined as Rankin grade 4 or 5. In a separate analysis defining poor outcome as Rankin grade 3, 4, or 5 the results were essentially the same.

The IVH was caused by SAH in 142 patients and by ICH in 201. In all studies on patients with SAH the aneurysm was clipped before fibrinolysis was initiated. Overall prognosis was worse in SAH patients. With regard to poor outcome, treatment effects of EVD with fibrinolysis tended to be greater in ICH patients than in SAH patients. These differences were not statistically significant.

We found only one complication from fibrinolytic treatment; in this patient with an ICH an increase in hematoma volume on computed tomography was found 16 h after infusion of fibrinolytic agents [19]. No data were available on the clinical condition of this patient at the time of the complication.

Table 2 Outcome data after intraventricular hemorrhage according to treatment and type of hemorrhage (*Ref* reference)

Therapy	*n*	Deaths				Poor outcome			
		n	%	RR	95% CI	*n*	%	RR	95% CI
Overall	343								
Conservative	176	139	78	Ref.	–	94/104	90	Ref.	–
EVD	118	69	58	0.74	0.55–0.99	105/118	89	0.98	0.75–1.30
EVD + Fibrinolysis	49	3	6	0.08	0.02–0.24	13/38	34	0.38	0.21–0.68
SAH	142								
Conservative	83	70	84	Ref.	–	62/67	93	Ref.	–
EVD	43	29	67	0.72	0.47–1.13	40/43	93	1.01	0.68–1.50
EVD + Fibrinolysis	16	0	–	–	–	8/15	53	0.58	0.28–1.20
ICH	201								
Conservative	93	67	72	Ref.	–	32/37	86	Ref.	–
EVD	75	42	56	0.78	0.53–1.14	65/75	87	1.00	0.66–1.53
EVD + Fibrinolysis	33	3	9	0.13	0.04–0.40	5/23	22	0.25	0.10–0.65

Discussion

The outcome is poor in patients with severe IVH caused by SAH or ICH if the intraventricular clot is left untreated. No randomized trials on treatment strategies for this intraventricular clot have yet been performed. In this meta-analysis of 18 studies we found that outcome after EVD plus fibrinolytic therapy was significantly better than after EVD without fibrinolytic therapy. Compared with conservative treatment, EVD without fibrinolytic therapy was associated with a lower case fatality rate, but not to a larger proportion of patients who returned to an independent life-style. There was only a single complication related to fibrinolytic therapy (2%); therefore we conclude that this therapy is reasonably safe.

Raw RR values and those adjusted for age, percentage of men, percentage of patients with poor WFNS grade, study design, and year of publication were essentially the same; however, the data required to make adjustments were lacking in some studies. Especially the proportion of patients with a poor WFNS grade on admission did not significantly affect outcome because these scores were comparable in all studies.

We defined poor outcome as Rankin score 4 or 5, but we have also conducted a sensitivity analysis with death and dependency defined as Rankin score of 3 or higher. The results were essentially the same.

Although the prognosis can differ between patients with SAH and those with ICH, the outcome for patients with severe ventricular extension was strikingly similar in patients with SAH and those with ICH if the intraventricular clot was left untreated. This similarity appeared to justify a pooled analysis of the treatment effect of fibrinolysis with EVD in the two categories of patients. Although there were differences between patients with SAH and patients with ICH in the effects of fibrinolytic treatment after EVD, the trend in risk reduction was the same for the two conditions.

Our results should be interpreted with caution because we compared nonrandomized treatment groups, and their prognostic profiles may hence differ markedly. The fact that the observed benefit of EVD plus fibrinolytic therapy was still present after adjusting for known differences between treatment groups supports the view that EVD plus fibrinolytic therapy is more effective than other strategies. However, selection bias with regard to unknown prognostic factors could not be excluded in our analysis.

Publication bias may have affected the results of this meta-analysis. Studies that found no effect of treatment on outcome may have been left unpublished because the public effect of the results would have been disadvantageous for investigators or sponsors. This would result in an overestimation of treatment effects. Because the effects of fibrinolytic treatment are so large, we assume that such bias affected the size of the effects but not the direction.

For this meta-analysis we had to depend on observational studies because no RCTs have yet been conducted. We attempted to be as thorough as possible in collecting relevant studies, but we cannot exclude the possibility that we overlooked some. For RCTs it is known that electronic searching combined with hand-searching of all references retrieves only about 65% of relevant trials. This percentage is probably is even lower for observational studies because editors are reluctant to accept small observational studies of treatment effects.

It has been speculated that intraventricular blood per se is not the cause of poor outcome, but that IVH is a manifestation of a great impact of the hemorrhage [17]. The poor outcome is then explained by this great impact of the hemorrhage. Nevertheless, our findings show that lysis of intraventricular blood clot combined with EVD is associated with better outcome in patients with severe IVH.

Thus, perhaps not all is lost in patients with a poor clinical condition and a hydrocephalus with IVH.

We conclude that EVD combined with fibrinolytic therapy is a promising treatment strategy for patients with severe IVH caused by SAH or ICH; the results indicate at least that this treatment is not dangerous. Several forms of bias probably influence the *magnitude* of the effect, but it is unlikely that these have also influence the *direction* of the effect. The several forms of bias result in a considerable uncertainty on the effectiveness of the treatment, and therefore randomization to no active treatment would be quite ethical. We feel that a randomized trial is warranted.

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